UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,984	05/08/2008	Jei Man Ryu	HANOL-12054	2429

72960 7590 09/23/2009

Casimir Jones, S.C.
440 Science Drive
Suite 203
Madison, WI 53711

EXAMINER	
PIHONAK, SARAH	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
09/23/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,984	RYU ET AL.	
	Examiner	Art Unit	
	SARAH PIHONAK	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 (national stage application) of PCT/KR05/03934, filed on 11/22/2005.

Priority

This application, filed on 5/8/2008, claims foreign priority to Application No. 10-2004-0096390, filed on 11/23/2004.

1. Claims 1-9 are pending.

2. Claims 1-9 are rejected.

Claim Rejections-35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 3 and 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating bone fractures and allergic inflammatory responses, does not reasonably provide enablement for preventing these conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. See M.P.E.P. 2164.08. The references of Lewiecki, *Clinical & Molecular Allergy*, **2**, pp. 1-11; and Tattersfield, *The Lancet*, **350**, S24-S27, are used in this rejection. It is noted that claims 3 and 5 are drawn to a formulation, and as such the

language of the claims which includes prevention of osteoporosis or allergic inflammatory diseases is not given patentable weight. However, even though this language is not considered relevant in determining patentability of these claims, the invention is still drawn to the prevention of these conditions, which necessitates this rejection.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to pharmaceutical compositions for preventing and treating osteoporosis, and preventing and treating allergic inflammatory disease. Thus, the claims taken together with the specification imply that osteoporosis and allergic inflammatory diseases can be prevented. The term 'prevention' has an absolute meaning, in that it implies that the condition can always, under all circumstances, be kept from occurring. Therefore, the breadth of the claims is broad, as they are drawn to the prevention of osteoporosis, and allergic inflammatory diseases, under all conditions.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

There is substantial evidence from the prior art that while the incidence of osteoporosis and inflammatory allergic conditions such as asthma can be reduced, a method for complete prevention of these conditions has not yet been established. Lewiecki teaches that there are multiple risk factors associated with the development of osteoporosis, such as family history, age, stature, nutrition, and other lifestyle factors (p. 3, right column, first paragraph). It is taught that while some of these risk factors can be minimized, such as with pharmacological agents and other efforts, some factors, such as advanced age, can not be removed (p. 3, right column, first paragraph). Lewiecki also teaches that while some medications have been shown to be effective in reducing vertebral fractures, only a few are able to reduce the incidence of hip fractures (p. 6, right column). Additionally, while many patients are responsive to therapy for osteoporosis, there exists a population which is not

responsive to pharmacological therapy or treatment, due to poor adherence to medication protocol or other existing health conditions (p. 9, left column, lower paragraph-right column, top paragraph). Therefore, while Lewiecki teaches that osteoporosis can often be effectively treated, there does not exist guidelines for the effective prevention of osteoporosis for all patient populations.

Tattersfield teaches that allergic inflammatory conditions, such as asthma, are often able to be treated, but as of yet there exists no cure (p. SII24, left column, top paragraph). Tattersfield also teaches that while many patients with asthma are able to be effectively treated, there still exists a patient population that is not able to have their symptoms reduced (p. SII24, right column, first paragraph). Additionally, Tattersfield teaches that considerable morbidity associated with asthma still exists (p. SII24, right column, lower paragraph-p. SII25, left column, top paragraph). Asthma is also caused by multiple factors involving genetic disposition and environment, and is more prevalent in urban communities (p. SII26, right column, first full paragraph-p. SII27, left column, top paragraph). Furthermore, Tatttersfield teaches that the correlation of specific risk factors to the development of asthma remains to be determined (p. SII27, left column, top paragraph). While asthma symptoms are often able to be effectively reduced with pharmaceutical agents and other interventions, there is no known cure for the condition, and a multitude of risk factors are involved in the development of asthma. As such, the prevention of asthma for all patient populations has yet to be realized.

(5) The relative skill of those in the art:

The relative skill of one in the art is expected to be high, such as that of an MD or other clinical specialist.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for the treatment of osteoporosis and some allergic inflammatory conditions.

However, the specification does not provide guidance for the prevention of osteoporosis or allergic inflammatory diseases.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to the lack of support for prevention of the conditions from the prior art and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Claim Rejections-35 USC § 102

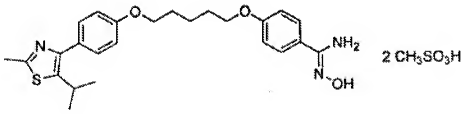
5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Suh, WO 03/007947. The reference of Suh was presented on the International Search Report.

The claims are drawn to an N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine 2 methanesulfonic acid salt, and compositions comprising the N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine 2 methanesulfonic acid salt and a pharmaceutically acceptable carrier. While claims 3, 4, and 5 cite that the composition is used for preventing and treating osteoporosis, treating bone fractures, and preventing and treating allergic inflammatory diseases, the claims are drawn to a composition. Therefore, the intended use of the composition was not given patentable weight, and was not considered in determining patentability of these claims.

The structure of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine 2 methanesulfonic acid salt is shown below:



Suh discloses that the compound, N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine, is effective in a composition for treating osteoporosis (p. 3, lines 23-31). Particularly, Suh teaches pharmaceutically acceptable salts of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine, and that salts of methanesulfonic acid are preferred (p. 4, lines 1-13).

Pharmaceutically acceptable carriers comprising the compound and salt forms of the compounds are also disclosed (p.4, lines 19-30). As Suh discloses the methanesulfonic acid salt of the instantly claimed compound, as well as pharmaceutically acceptable carriers, Suh anticipates the instant claims.

While Suh does not explicitly disclose preparation of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine 2 methanesulfonic acid by reacting N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine with methanesulfonic acid in a solvent, the methanesulfonic acid salts of the compound are disclosed. Therefore, it is inherent that to form N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine 2 methanesulfonic acid, the compounds N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine and methanesulfonic acid must be undergo a reaction.

Claim Rejections-35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suh, WO/007947, as applied to claims 1 and 3-5, in view of Hirano et. al., US Patent Application 2004/0019045.

The claims are directed to an oral formulation comprising N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine 2 methanesulfonic acid salt, an inorganic excipient such as calcium carbonate, and a disintegrant such as sodium starch glycolate or sodium croscarmellose.

As discussed supra, Suh discloses methane sulfonic acid salts of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine, as well as pharmaceutically acceptable carriers. Suh also teaches that the composition is administered orally (p. 4, line 31-p. 5, line 3). While Suh teaches that excipients are

present in the composition (p. 4, lines 25-30), excipients such as calcium carbonate and sodium croscarmellose are not explicitly taught.

Hirano et. al. teaches compounds and compositions for pharmaceutical utility, such as treating bone loss, osteoporosis, and promotion of bone formation (Abstract; p. 2, paragraph [0022]). Hirano et. al. teaches that the composition can be prepared for oral administration, as tablets, liquids, powders, capsules, etc. (p. 24, paragraphs [0359-0361]). Hirano et. al. also teaches that excipients suitable for oral administration include calcium carbonate, as well as disintegrants such as croscarmellose sodium and sodium starch glycolate (p. 24, paragraphs [0364] and [0366]).

Suh teaches the composition comprising the methane sulfonic acid salt of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine and pharmaceutically acceptable carriers and excipients for oral administration to treat osteoporosis. Hirano et. al. teaches compositions for treating ailments such as bone loss, osteoporosis, and to promote bone formation with excipients such as calcium carbonate and sodium starch glycolate for oral administration. One of ordinary skill in the art would have been motivated, at the time of the invention, to add excipients such as calcium carbonate and sodium starch glycolate to the composition taught by Suh for oral administration, because Hirano et. al. teaches that such excipients are commonly present in pharmaceutical compositions for oral administration. Additionally, as the composition taught by Hirano et. al. is also used to treat conditions such as osteoporosis and bone loss, one of ordinary skill in the art would have expected that the excipients used in the oral formulation would also be equally beneficial for the

composition taught by Suh, which is also effective for treating the same conditions. Therefore, the claimed invention would have been prima facie obvious to one of ordinary skill in the art, at the time of the invention, in view of Suh and Hirano et. al.

Claim Rejections-Obviousness Type Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1 and 3-9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 11/577469. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to compositions and formulations comprising N-hydroxy-4-{5-[4-(5-isopropyl-2-

methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine 2 methanesulfonic acid, and excipients such as calcium carbonate and croscarmellose sodium.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are drawn to N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine 2 methanesulfonic acid, and compositions and formulations comprising this compound, along with a carrier and excipients such as calcium carbonate and croscarmellose sodium. The co-pending claims are drawn to an oral preparation comprising pharmaceutically acceptable salts of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine, as well as excipients such as calcium carbonate and croscarmellose sodium. The co-pending claims are also drawn to ratios of the carbonate to the salt of N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine, in an amount from 0.4 to 6 parts by weight to one part by weight, as well as the ratio of the disintegrant to N-hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine ranging from 0.5 to 5 parts by weight to one part by weight. Tablets, capsules, and granule forms are also included in the co-pending claims. While the instant claims do not explicitly include the weight ratio limitations or the tablet, capsules, or granule forms, such weight ratios would have been obvious in the development of stable formulations, and tablet and capsule forms would have been obvious for oral formulations. Therefore, as both sets of claims are drawn to compositions and oral formulations comprising N-hydroxy-4-{5-[4-

(5-isopropyl-2-methyl-1,3-thiazol-4-yl)phenoxy]pentoxy} benzamidine 2 methanesulfonic acid and excipients, the claims are not patentably distinct from each other.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached on Monday-Thursday 8:00 AM - 6:30 PM EST, with Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

S.P.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617